BIRTH DEFECT RISK FACTOR SERIES:

- TRIPLOIDY

DESCRIPTION

Triploidy is a chromosomal abnormality where three complete sets of the haploid genome instead of the normal two sets are present. In other words, in humans there are 69 chromosomes instead of the normal 46 chromosomes. The most common triploidy karyotypes and their distribution are presented in Table 1. The low frequency of 69,XYY suggests that either the process by which this karyotype occurs is uncommon or the karyotype has lower survivability than the other karyotypes.

Triploidy may occur with aneuploidies, resulting in complex karyotypes (e.g., karyotype 70,XXY,+21). Triploidy may also be found with mosaicism, where some cells in the body have a triploid chromosome complement and other cells in the body have a different chromosome complement, either normal diploid (e.g., karyotype 69,XXY/46,XX) or abnormal (e.g., karyotype 69,XXY/70,XXY,+21).

Table 1. Distribution of triploidy cases represented by karyotype* in several studies

Study	69,XXX	69,XXY	69,XYY
Daniel et al., 2001	42%	58%	0%
McFadden et al., 2000	49%	49%	2%
Miny et al., 1995	41%	59%	0%
Neuber et al., 1993	41%	57%	2%
Ohno et al., 1991	37%	63%	0%
Uchida et al., 1985	43%	55%	2%
Jacobs et al., 1982	31%	68%	1%
Niebuhr, 1974	36%	60%	3%

*Includes mosaicisms and variations where another form of aneuploidy occurs along with the triploidy

Etiology

Three different mechanisms may produce triploidy:

1) nondisjunction in meiosis I or meiosis II of spermatogenesis (sperm formation), resulting in an extra set of paternal chromosomes (diandry)

2) nondisjunction in meiosis I or meiosis II of oogenesis (egg formation), resulting in an extra set of maternal chromosomes (digyny)

3) double fertilization of a normal egg, resulting in an extra set of paternal chromosomes (dispermy)

One investigation reported that mechanism 1 accounted for 23.6% of triploidy cases, mechanism 2 for 10%, and mechanism 3 for 66.4% (Jacobs et al., 1978).

As shown in Table 2, a number of studies, particularly older studies, found that the majority of triploidy cases were of paternal origin (Daniel et al., 2001; Redline et al., 1998; Uchida et al., 1985; Jacobs et al., 1982; Jacobs et al., 1978; Kajii and Niikawa, 1977) while more recent studies found the majority of triploidy cases to be of maternal origin (Baumer et al., 2000; McFadden et al., 2000; McFadden et al., 1993). Paternal origin for triploidy is higher at certain gestational ages while maternal origin for triploidy is higher at other gestational ages (McFadden et al., 2000; Zaragoza et al., 2000). Thus the wide variation in parental origin between the various studies may be due to the studies using cases derived from difference stages of fetal death.

Table 2. Parental origin of the extra set of chromosomes in triploidy reported by various studies

Study	Maternal origin (%)	Paternal origin (%)

Study	Maternal origin (%)	Paternal origin (%)
Daniel et al., 2001	39%	61%
Baumer et al., 2000	80%	20%
McFadden et al., 2000	63%	37%
Redline et al., 1998	34%	66%
Miny et al., 1995	71%	29%
McFadden et al., 1993	75%	25%
Uchida et al., 1985	36%	64%
Jacobs et al., 1982	33%	77%
Jacobs et al., 1978	15%	85%
Kajii and Niikawa, 1977	13%	88%

Most cases of triploidy due to paternal origin result from dispermy (Baumer et al., 2000; Zaragoza et al., 2000; Kajii and Niikawa, 1977). Several studies have reported that the majority (62-77%) of cases of triploidy of maternal origin result from nondisjunction in meiosis II (McFadden et al., 2000; Zaragoza et al., 2000; Jacobs et al., 1982), although another investigation found the nondisjunction to be evenly distributed between meiosis I and meiosis II (Baumer et al., 2000).

Maternal age has not been found to be associated with any of the three mechanisms by which triploidy occurs (Baumer et al., 2000). One investigation observed that the XXX/XXY ratio changes from 1:2 to 2:1 and proportion of hydatidiform moles (triploidy of paternal origin) decreases with increasing maternal age, indicating that digyny is more important for older women and diandry more important for younger women (Neuber et al, 1993).

One study identified no association between parental origin of the triploidy and phenotype (Kajii and Niikawa, 1977). However, more recent studies reported paternal origin but not maternal origin to be associated with the hydatidiform mole phenotype of triploidy, although parental origin does not always result in hydatidiform mole (Zaragoza et al., 2000; Redline et al., 1998).

Phenotype

There is wide variation in the clinical features associated with triploidy, ranging from a normal phenotype to multiple major birth defects.

Cases of triploidy are grouped into two fetal and placental phenotypes that roughly correspond to the parental origin of the extra set of chromosomes (McFadden and Kalousek, 1991):

Type I: well-formed fetus with a normal or microcephalic head and a large placenta with cystic changes - associated with diandry

Type II: fetus with growth restriction and a large head and a small, noncystic placenta - associated with digyny

Various literature describe the birth defects and other abnormalities associated with triploidy (Sergi et al., 2000; Doshi et al., 1983; Wertelecki et al., 1976). These anomalies include fetal growth restriction, partial hydatidiform mole (the placenta and fetus are partially comprised of vesicular villous structures resembling grapes), macrocephaly, hydrocephaly, holoprosencephaly, micrognathia, microphthalmia, bulbous nose, small mouth, malformed and low set ears, coloboma of the eye, cataracts, cleft lip and/or palate, syndactyly of the third and fourth digits of the hands or feet, simian crease of the hand, rocker bottom feet, ventricular septal defects, atrial septal defects, pulmonary hypoplasia, diaphragmatic hernia, intestinal malrotation, cystic kidney, adrenal hypoplasia, ovarian hypoplasia, and abnormal male genitalia (hypospadias, micropenis, undescended testicles). Neural tube defects may be found in 25% and abdominal wall defects in 10-18% of triploidy cases.

Cases with diploid/triploid mosaicism tend to have a milder phenotype than completely triploid cases, but usually suffer from mental retardation (Tantravahi et al., 1986).

Prenatal diagnosis

Triploidy may be prenatally diagnosed through cytogenetic analysis of cells obtained through such procedures as amniocentesis and chorionic villus sampling.

Fetal nuchal translucency in the first trimester is frequently increased for fetuses with triploidy (Spencer et al., 2000; Jauniaux et al., 1997; Pandya et al., 1995). Triploidy has been associated with elevated materal serum alpha fetoprotein (AFP) and total and beta human chorionic gonadotropin (hCG) levels and low maternal serum pregnancy-assisted plasma

(AFP) and total and beta-human chorionic gonadotropin (hCG) levels and low maternal serum pregnancy-assisted plasma protein-A (PAPP-A) levels in the first trimester (Spencer et al., 2000; Jauniaux et al., 1997). However, first-trimester nuchal translucency and maternal serum screening is not routinely performed in the United States.

Triploidy has been associated with two distinct patterns of maternal serum AFP, hCG, and estriol levels in the second trimester (Benn et al., 2000; Schmidt et al; 1994; Canick and Saller, 1993; Fejgin et al., 1992; Mason et al., 1992; Oyer and Canick, 1992; Kohn et al., 1991; Freeman et al., 1989; Pircon et al., 1989a; O'Brien et al., 1988):

1) elevated AFP, elevated hCG, and low or normal estriol

2) low or normal AFP, low hCG, and low estriol

Second-trimester amniotic fluid AFP has been reported to be normal in the presence of triploidy except when there is also an open neural tube present (Freeman et al., 1989). (See table 3 for a review of maternal serum marker levels and nuchal translucency in relation to triploidy.) However, second-trimester maternal serum screening in the United States does not systematically screen for triploidy. Moreover, one investigation found that the proportion of triploidy cases in a population at increased risk of Down syndrome as a result of maternal serum screening was not greater than expected for the general population (Ryall et al., 2001). And fetuses with triploidy typically do not have a consistent pattern of abnormalities on prenatal ultrasound (Pircon et al, 1989b).

Thus cases of triploidy will frequently be prenatally diagnosed incidentally as a result of cytogenetic analysis for other reasons such as advanced maternal age.

Table 3. Maternal serum marker and nuchal translucency levels in pregnancies with triploidy

Trimester	AFP	total hCG	uE3	beta-hCG	PAPP-A	NT
First	high	high	-	high	low	high
Second	high	high	low/normal			
	low/normal	low	low			

AFP - alpha-fetoprotein

hCG - human chorionic gonadotropin

uE3 - estriol

PAPP-A - pregnancy-assisted plasma protein-A

NT - nuchal translucency

Mortality/survival

Triploidy is lethal, with no survivors reported beyond 10.5 months of age (Sherard et al., 1986). Postnatal survivors usually have the type II phenotype with the extra chromosomes of maternal origin (Hasegawa et al., 1999; Graham et al., 1989).

Infants with triploid/triploid mosaicism will have longer survival than infants with true triploidy (Tantravahi et al., 1986).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Sex

The sex ratio of triploidy is linked to the distribution of sex chromosomes (table 1). Males account for 51-69% of triploidy cases (McFadden et al., 2000; Miny et al., 1995; Neuber et al., 1993; Ohno et al., 1991; Uchida et al., 1985; Jacobs et al., 1982).

Parental age

Neither maternal nor paternal age have been associated with triploidy risk (Ford et al., 1996; Rochon and Vekemans, 1990; Uchida et al., 1985; Niebuhr, 1974). However, as outlined in the Etiology section, maternal age does appear to be related to the type of triploidy (Neuber et al, 1993).

Diabetes

One investigation found no association between maternal gestational diabetes and triploidy (Moore et al., 2002).

Other

Animal studies have identified increased risk of triploidy with **colchicine** (an alkaloid used to treat gout), **hypoxia**, and **heat shock** (Niebuhr, 1974).

One study reported that 50% of mothers of triploidy conceptuses had preconceptional **abdominal radiation** exposure (Uchida and Freeman, 1985).

Triploidy has also been potentially linked to **delayed fertilization** resulting from prolonged menstrual cycles or the cessation of oral contraceptives (Niebuhr, 1974). Triploidy has been reported in conceptuses resulting from **in vitro fertilization** (Angell et al., 1986; Ulmer et al., 1985) and in conceptuses of women who have **recurrent miscarriages** (Carp et al., 2001).

PREVALENCE

Triploidy has been estimated to occur in 1-2% of all clinically recognized conceptions (Jacobs et al, 1978). However, the majority of triploidy conceptuses do not survive to term. It has been assessed that only one-third of triploidy conceptuses survive past 15 weeks gestation (Warburton et al., 1994) and that for every triploidy conceptus that survives to term, approximately 1200 conceptuses result in fetal death (Doshi et al., 1983).

Triploidy has been reported in 1-13% of spontaneous abortions that were studied (Redline et al., 1998; Ford et al., 1996; Kalousek et al., 1993; Neuber et al., 1993; Ohno et al., 1991; Shepard et al., 1989). Triploidy is found in 8/10,000 chorionic villus samplings (Association of Clinical Cytogeneticists Working Party on Chorionic Villi in Prenatal Diagnosis, 1994) and 4/10,000 amniocenteses (Horger et al., 2001).

The live birth rate for triploidy is 1/10,000 live births (Jacobs et al., 1982; Jacobs et al., 1974).

As a result of prenatal diagnosis, a portion of triploidy fetuses will be electively terminated. An investigation in Europe reported an elective termination rate of 82% for triploidy (De Vigan et al., 2001). One study reported 100% of fetuses prenatally diagnosed with triploidy were electively terminated (Horger et al., 2001).

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